Declaration

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Rhonda A. Etienne 2/10/03
Rhonda A. Etienne Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael B. Foster
Serial Number:	09/838,968
Filed:	April 20, 2001
Art Unit:	1653
Confirmation No.:	1662
Examiner:	Kam, Chih Min
Title:	**METHOD OF OPTIMIZING GROWTH HORMONE REPLACEMENT**
Attorney Ref. No.:	RENAS-03

Cincinnati, Ohio 45202 February 10, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION OF MICHAEL B. FOSTER, M.D. PURSUANT TO 37 CFR §1.132

I, MICHAEL B. FOSTER, M.D., declare as follows:

1. I am the inventor of the above-identified patent application.

2. I received my degree as a Doctor of Medicine from University of Tennessee in the year 1975. I have 23 years of experience in the field of

endocrinology, and 23 years of experience in the field of human growth hormone therapy, which is the subject of this application. I have read the outstanding Office Action and understand the position of the Examiner.

3. I respectfully disagree with the Examiner's finding that the indicated claims are indefinite because of the term "said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability date" or "said dose producing said optimal response is calculated from a daily dose to a monthly dose based on individualized bioavailiability data".

4. One skilled in the art knows how to use bioavailability data to calculate a dose of an agent. In this case, the maintenance dose of hGH from a daily dose to a monthly dose is based upon individualized bioavailability data. The specification discloses that the individual's response to serially increased doses of hGH are evaluated, usually over one to two months. The dose is adjusted at about two to four week intervals, and in a range equal to that of the initial dose. The specification also provides examples of these calculations. It teaches that a male receives an initial dose of 2 μg/kg/day for two to four weeks, then receives a dose of 6 μg/kg/day for two to four weeks, then receives a dose of 8 μg/kg/day for two to four weeks, etc., until the maintenance dose is achieved. It also teaches that a female receives an initial dose of 4 μg/kg/day, then receives a serially increased dose of 8 μg/kg/day for two to four weeks, then receives a dose of 12 μg/kg/day for two to four weeks, etc., until the maintenance dose is achieved. The specification also teaches that, once the

maintenance dose is achieved, a monthly dose of hGH is administered, such as in a microsphere formulation. The specification discloses that microsphere formulations have 10-20% less bioavailability than daily dose formulations, and that this must be taken into account. Such determinations are performed by and known to one skilled in the art.

5. I respectfully disagree with the Examiner's finding that each of the Drake and Murray references anticipate my claimed invention.

6. Both Drake and Murray define that the established definition for an "optimal" dose of growth hormone is based on age- and gender-specific norms for IGF-1 levels. There is, however, wide variation, from study to study, as to where the range for the target IGF-1 level is set. The range of IGF-1 levels as disclosed in each of Drake and Murray is manifestly one that allows for undesirable and, in many cases, harmful alterations in structure and in physiologic function of tissues in the body after about age 30. For example, there is loss of lean body mass, loss of muscle function, increase in fat mass, decreased bone density, etc.

7. In contrast, the claimed method determines an individualized dose, allowing a target for IGF-1 levels in a range in which the above-described negative changes have not yet begun to occur. Thus, the claimed method prevents and/or reverses these changes. Neither Drake nor Murray disclose selecting a dose producing an optimal replenishment, as claimed.

8. I respectfully disagree that Drake anticipates my invention. Drake discloses a "dose titration regimen based solely on restoration of serum IGF-1 to the upper part of the age-related reference range" (emphasis added). This is a uniform titration regimen, based on a defined target range of serum IGF-1. My invention discloses an individualized dose, not a defined target. The claims further recite steps for determining this individualized dose.

9. Drake discloses lock-step increases of unvarying magnitude. In contrast, I claim serially increased doses of the composition; the increase, then, depends upon the initial dose administered. Thus, Drake does not disclose serially increased doses.

10. I also respectfully disagree that Murray anticipates my invention. Murray states "The ideal dosing regimen and determinants of the maintenance dose have, however, yet to be elucidated." In contrast, my invention provides these "ideal dosing regimen and determinants of maintenance dose".

11. More specifically, Murray's statement that "the ideal dosing regimen and determinants of the maintenance dose have, however, yet to be elucidated" is an opinion. However, the claimed method produces an optimal clinical response while avoiding side effects. In my opinion, this is a reasonable definition of the "ideal regimen" desired by Murray. The debate among endocrinologists about the efficacy of hGH therapy in addressing issues like declining bone density is founded in their lack of appreciation that their target for the therapeutic response is set too low (and they

invariably ratchet up the dose too quickly, accounting for the incidence of side effects that they report).

12. Further, Murray has statistically analyzed the data to be able to assert that baseline IGF-1 levels predict maintenance hGH dose. In my opinion, a careful analysis of the data indicate otherwise. Specifically, it is not the IGF-1 which predicts the hGH dose, rather, it is the presence of the effect of estrogen which predicts the dose. Murray's so-called predictive value is created by the fact that the estrogen-using female subjects cluster at the bottom end of the distribution of IGF-1 levels, and they certainly do require significantly higher doses of hGH to generate a given IGF-1 response compared to a population of GH deficient men, particularly men taking testosterone. If estrogen is not a consideration, there is no apparent predictive effect of Murray's baseline IGF-1 level on eventual hGH dose. In contrast, the invention has accounted for this effect of estrogen, particularly orally administered estrogen.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

31 Jan 03

Date

Michael B. Foster, M.D.